32. (Amended) A [cell] library of cells according to claim 1 or 2, wherein at least one of said enzymes further comprises a fusion partner.

34. (Amended) A [cell] library of cells according to claim 31, wherein said fusion partner is a targeting sequence.

39. (Amended) A [cell] library of cells according to claim 32, wherein said fusion partner is a targeting sequence.

REMARKS

Claims 1-8 and 27-42 are pending.

Claims 9-26 are cancelled.

Claims 29-30, 33, 35-38, and 40-42 are withdrawn from consideration.

Claims 1-8, 27, 28, 31, 32, 34 and 39 are pending and are being examined on their merits. Pending Claims 1-8, 27, 28, 31, 32, 34 and 39 are enclosed as an attachment.

Support for the amendment of claims 1-8, 27, 28, 31, 32, 34 and 39 reciting 'library of cells, each cell comprising a different composition' is found both implicitly and explicitly within the specification; see e.g., on page 32, lines 16 to 20.

Support for the amendment of claims 1 and 2 reciting 'wherein said enzymes do not biologically react with said scaffold' is found in the specification, e.g., on page 4, lines 4-5 and in original claim 21.

Support for the amendment of claim 1 reciting 'capable of being bound' is found e.g., in claim 2 and within the specification on page 3 lines 11-12.

Support for the amendment of claim 8 reciting 'wherein said agent precursor is from a library of synthetic compounds' is found in the specification, e.g., on page 34, lines 18-19.

Further, claims 1 and 2 were amended for clarity.

New matter has not been introduced by way of amendment.

Election/Restriction:

The Examiner requested clarification concerning the status of the pending claims.

Applicants submit that in response to a restriction/election requirement, mailed March 30,1998, Applicants elected claims 1-8 (see response mailed May 26, 1999). The election was made without traverse.

Applicants wish to draw the Examiner's attention to the Office Action, mailed August 26, 1998, wherein the Examiner states "[c]laims 9-26 stand withdrawn from consideration". Claims 9-26 are cancelled herein.

In Applicants' response to the Office Action, mailed August 26, 1998, new claims 27-42 were added (see response mailed December 28, 1998).

In response to a second restriction/election requirement, mailed March 24,1999, Applicants elected species corresponding to claims 28, 34, and 39 (see response mailed May 26, 1999), in addition to claims 1-8, 27, 31 and 32.

Based upon the foregoing, claims 1-8, 27, 28, 31, 32, 34, and 39 are presented for examination.

The rejection of claims 1-8, 27-28, 31-32, 34, and 39 under 35 U.S.C. §112, first paragraph:

The Examiner rejects claims 1-8, 27-28, 31-32, 34, and 39 under §112 for reciting "exogenous scaffolds having no enzymatic activity". Applicants have amended the above cited claims including the deletion of the rejected phrase "having no enzymatic activity". Applicants submit that the claims now conform to the requirement of §112, first paragraph. Accordingly, the rejection of record should be withdrawn.

The rejection of claims 1-8, 27-28, 31-32, 34, and 39 under 35 U.S.C. §112, second paragraph:

The Examiner considers claim 8 indefinite by reciting "an exogenous bioactive agent precursor" and states that it is not possible to determine what is or is not "a bioactive agent precursor". Without admitting the proprietary of the rejection, Applicants have amended claim

8 to recite "an exogenous bioactive agent precursor, wherein said agent precursor is from a library of synthetic compounds." Applicants submit that the metes and bounds of a 'library of synthetic compounds' is known to the skilled artisan.

The Examiner rejects claims 31-32, 34, and 39 as being vague and indefinite for reciting the term "fusion partner". Applicants submit that the definition of the term "fusion partner", found both implicitly and explicitly within the specification; see e.g., on page 16, lines 15-26, is not vague and not indefinite.

> "In addition to the coding sequences for the scaffolds and enzymes, the nucleic acids of the invention may include fusion partners. By "fusion partner" herein is meant a sequence that is associated either with the nucleic acid or the expression product that confers a common function or ability. Fusion partners can be heterologous (i.e. not native to the host cell), or synthetic (not native to any cell). Suitable fusion partners include, but are not limited to: 1) targeting sequences, defined below, which allow the localization of the scaffolds and enzymes into a subcellular or extracellular compartment; 2) rescue sequences, as defined below, which allow the purification or isolation of either the scaffolds and enzymes or the nucleic acids encoding them; 3) stability sequences, which confer stability or protection from degradation to the scaffolds and enzymes or the nucleic acids encoding them, for example resistance to proteolytic degradation; or 4) combinations of any of 1), 2) and 3)."

Further, Applicants discloses on several fusion partners, e.g., targeting sequences (page 16, line 27 - page 22, line 11), rescue sequences (page 22, lines 12-22), stability conferring sequences (page 22, line 23 - page 23, line 3), and linker or tethering sequences (page 23, lines 6-23). In addition the specification discloses on page 23, lines 4-5:

> "The fusion partners may be placed anywhere (i.e. N-terminal, C-terminal, internal) in the structure as the biology and activity permits."

and on page 23, lines 24-28:

> "In a preferred embodiment, combinations of fusion partners are used. Thus, for example, any number of combinations may be used, with or without linker sequences. As is described herein, using a base vector that contains a cloning site for receiving the enzyme and/or scaffold coding regions, one can cassette in various fusion partners 5' and 3' of the coding region."

Thus, given the specification, a skilled artisan does appreciate what is meant by the term "fusion partner" and as such, would use this term as claimed by the Applicants. Applicants submit that the skilled artisan understands what is encompassed by the claims, and can identify the subject matter as claimed.

The Examiner rejects claims 1-8, 27-28, 31-32, 34, and 39 as vague and indefinite for reciting the term "exogenous scaffold." Applicants submit that the definition of the term "exogenous scaffold,"found both implicitly and explicitly within the specification; see e.g., on page 13, lines 11-19, is not vague and not indefinite.

> "When the novel compositions are introduced into cells as is outlined below, the scaffolds are preferably exogeneous scaffolds. By "exogeneous scaffold" herein is meant that the scaffold either a) does not naturally occur within the cell, or b) does naturally occur within the cell but is present at a either a significantly higher concentration than is normally seen within the cell or in a form not normally seen in the cell; e.g. is a portion of a naturally occurring protein or nucleic acid sequence. In a preferred embodiment, the exogeneous scaffolds are synthetic; i.e. they do not naturally occur in nature. In some embodiments, it may be possible to alter endogeneous scaffolds such as actin chemically to produce novel scaffolds."

Further, Applicants disclose in the specification, e.g., on page 13, line 20 to page 16, line 14, the binding of enzymes to the scaffold, the kind of enzymes that can be used to bind to the scaffold. A skilled artisan does appreciate what is meant by the term "exogenous scaffold" and as such, would use this term as claimed by the Applicants. Thus, Applicants submit that the skilled artisan understands what is encompassed by the claims, and can identify the subject matter as claimed.

Further, Applicants respectfully remind the Examiner that an applicant may be his or her own lexicographer, defining terms as he or she wishes [see *Intellicall, Inc.* v. *Phonometrics, Inc.*, 21 USPQ 2d 1383 (Fed. Cir. 1992)]. Thus, the definitions of the terms, given both implicitly and explicitly within the specification clearly define a "fusion partner" and an "exogenous scaffold" as claimed.

Applicants believe that the above comments do address every issue raised under §112, second paragraph, and that the specification and claims provide the required enablement. Accordingly, the rejections are improper and Applicants respectfully request withdrawal of the rejections.

The rejection of Claims 1-8, 27-28, 31-32, 34, and 39 under 35 U.S.C. §101:

The Examiner rejects claims 1-8, 27-28, 31-32, 34, and 39 as being directed to non-statutory subject matter. Applicants respectfully traverse.

Applicants have amended the claims, including reciting "A library of cells, each cell comprising a different composition comprising...". Accordingly, the rejection of record should be withdrawn.

The rejection of Claims 1-8, 27-28, 31-32, 34, and 39 under 35 U.S.C. §102(e):

The Examiner rejects claims 1-8, 27-28, 31-32, 34, and 39 as being anticipated by Khosla et al. (US 5,672,491). Without admitting the proprietary of the rejection, Applicants have amended the claims to further recite that "wherein said enzymes do not biologically react with said scaffold."

As argued previously, Khosla et al. teach the synthesis of polyketides by the multi-enzyme complex 6-deoxyerythronolide B synthetase (DEBS) consisting of three different proteins. The authors construct expression vectors encoding these three proteins, introduce them into host cells, which do not contain the corresponding endogenous genes and demonstrate that polyketides are made. Figure 9 of Khosla et al. shows the gene organization and the modular structure for the three proteins which constitute the multi-enzyme complex DEBS.

The Examiner interprets the disclosure of Khosla et al. as evidence that the three proteins bind or interact with each other to form DEBS. Further, according to his interpretation, one of the three proteins functions as a scaffold and provides binding sites for the

other two proteins. As such, the Examiner contends, the subject matter of the claims is anticipated by Khosla et al.

Applicants respectfully disagree with the Examiner's interpretation.

First of all, while Khosla et al. express the three proteins and demonstrate enzymatic activity, they do not demonstrate that the three recombinant proteins assemble into a multi-enzyme complex comprising the three proteins. That is, the structure of the DEBS multi-enzyme complex has not been determined yet. Thus, contrary to the Examiner's assumption, it is not known if one of the three proteins provides binding sites for the other two proteins. It is equally likely that protein 1 provides a binding site for protein 2 and protein 2 provides a binding site for protein 3. In this scenario, whichever protein is considered being a scaffold, this scaffold does not provide "at least a first binding site and a second binding site" to which a "first enzyme" and a "second enzyme" can bind, as recited in the claims.

As the Examiner is aware, inherency is not a permissive consideration on which to base obviousness. "That which may be inherent is not necessarily known. Obviousness cannot be predicted on what is unknown." In re Spormann, 150 USPQ 449, 452 (CCPA 1966).

Secondly, as is known in the art, the DEBS multi-enzyme complex consists of three proteins, each comprising modules. Each of the proteins adds two-carbon building blocks to the polyketide and performs chemical modification to the chain before transferring it to the next part of the enzyme (see also Figure 9 in Khosla et al.). Even assuming, arguendo, that one protein of the DEBS complex (protein 1) provides at least a first binding site for protein 2 and a second binding site for protein 3, such a complex is not anticipated by the claims as amended. Within the DEBS complex, protein 2 or protein 3 or both (which, according to the Examiner's interpretation, correspond to enzymes 1 and 2 of the instant application) biologically react with protein 1 (which, according to the Examiner's interpretation, corresponds to the scaffold of the instant application) by accepting a substrate for further modification. This is not the case in the present invention. The amended claims clearly recite that the enzymes, which bind to the scaffold, do not biologically react with said scaffold.

In summary, Applicants submit that the claimed subject matter is not anticipated by Khosla et al. and respectfully request reconsideration and withdrawal of the rejection.

The rejection of claims 1-8, 27-28, 31-32, 34, and 39 under 35 U.S.C. §102(b):

The Examiner rejects claims 1-8, 27-28, 31-32, 34, and 39 as being anticipated by Horowitz as evidenced by the teachings of Zhao and Padmanabahn (New Biol. 1991).

Horowitz teaches adenoviruses that infect mammalian cells. The Examiner's position appears to be that adenoviral genome is an exogenous scaffold, and has binding sites, for example for adenoviral DNA and RNA polymerases. However, even assuming arguendo, that this could be true, both the DNA polymerase and the RNA polymerase are enzymes that biologically react with the adenoviral genome: the DNA polymerase biologically reacts with the adenoviral genome to produce DNA copies and the RNA polymerase biologically reacts with the adenoviral genome to produce mRNAs encoding adenoviral proteins.

Zhao and Padmanabahn (New Biol. 1991) disclose three basic amino acid clusters in the adenovirus DNA polymerase, designated BS I, BS II, and BS III, respectively. These clusters comprise a novel bipartite nuclear localization signal, which, when fused to a heterologous protein, such as E. coli beta-galactosidase, targeted the fusion protein to the nucleus.

For an invention to be anticipated under 35 U.S.C. §102(b), the cited reference must teach "each and every element" of the claim (MPEP §2131).

Applicants submit that the amended claims 1 and 2 and the respective dependent claims are not anticipated by the references cited. None of the references teach a library of cells, nor that the enzymes do not biologically interact with an exogenous scaffold. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of record.

Additional points raised by the Examiner:

Examiner's point #17 is unclear. Based upon Applicants' detailed response to the previous Office Action, in which claims 1-8 were rejected under §103(a) over Bott et al. and the fact that the Examiner did not reinstate this rejection, it is Applicants' belief that this rejection is overcome.

Examiner's point #18, referring to the Ricard et al. reference is noted by the Applicants. However, as no complete reference was provided and no objection/rejection was raised based upon this reference, no further comments are provided herein.

Examiner's point #19, referring to the identical disclosure in WO 95/08548 and US 5,672,491 is noted by the Applicants.

With respect to the Examiner's point #20, Applicants resubmit form 1449, which was filed to accompany the supplemental IDS filed 3/25/99 and received in the PTO on March 29, 1999, as evidenced by the PTO stamped return postcard (see enclosed copy).

The Applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited.

If after review of this amendment, the Examiner has further unresolved issues, the Examiner is respectfully requested to phone the undersigned, Robin Silva, at (415) 781-1989.

Respectfully submitted,

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APPENDIX

1. (Twice Amended) A library of cells, each cell comprising a different composition comprising:

a) an exogenous scaffold comprising at least a first binding site and a second binding site; and

b) at least a first enzyme and a second enzyme, wherein at least one of said enzymes is heterologous to said cell;

wherein said first enzyme is capable of being bound to said first binding site and said second enzyme is capable of being bound to said second binding site and wherein said enzymes do not biologically react with said scaffold.

2. (Twice Amended) A library of cells, each cell comprising a different composition comprising:

a) nucleic acid encoding an exogenous scaffold comprising at least a first binding site and a second binding site; and

b) nucleic acid encoding at least a first enzyme and a second enzyme, wherein at least one of said enzymes is heterologous to said cell;

wherein said first enzyme is capable of being bound to said first binding site and said second enzyme is capable of being bound to said second binding site and wherein said enzymes do not biologically react with said scaffold..

3. (Amended) A library of cells according to claim 1 or 2, wherein said scaffold comprises at least three binding sites.

4. (Amended) A library of cells according to claim 1 or 2, wherein said scaffold comprises at least four binding sites.

5. (Amended) A library of cells according to claim 1 or 2, wherein said scaffold comprises at least five binding sites.

6. (Amended) A library of cells according to claim 1 or 2, wherein said binding sites are on the same scaffold molecule.

7. (Amended) A library of cells according to claim 1 or 2, wherein said binding sites are on different scaffold molecules.

8. (Twice Amended) A library of cells according to claim 1 or 2, further comprising

c) an exogenous bioactive agent precursor, wherein said agent precursor is from a library of synthetic compounds.

27. (Amended) A library of cells according to claim 1 or 2, wherein said cell is a mammalian cell.

28. (Amended) A library of cells according to claim 1 or 2, wherein said scaffold is linear.

31. (Amended) A library of cells according to claim 1 or 2, wherein said scaffold further comprises a fusion partner.

32. (Amended) A library of cells according to claim 1 or 2, wherein at least one of said enzymes further comprises a fusion partner.

34. (Amended) A library of cells according to claim 31, wherein said fusion partner is a targeting sequence.

39. (Amended) A library of cells according to claim 32, wherein said fusion partner is a targeting sequence.